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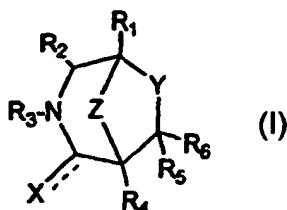
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(54) Title: 3-AZA-6,8-DIOXABICYCLO[3.2.1]OCTANES AND ANALOGUES AND COMBINATORIAL LIBRARIES

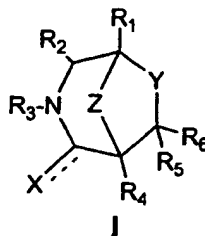


(57) Abstract: The present invention relates to new highly functionalized heterobicycle derivatives of general formula (I), prepared by a process which involves only two steps by using, as starting products, commercially available, or easily prepared, α -amino ketones and α,β -dihydroxy acids or α -amino- β -hydroxy acids or α -hydroxy- β -amino acids or α,β -dithiol acids derivatives and to libraries containing compounds of formula (I) and to the generation of such combinatorial libraries composed of compounds of formula (I), in individual synthesis, mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or automated fashion.

3-AZA-6,8-DIOXABICYCLO[3.2.1]OCTANES AND ANALOGUES AND COMBINATORIAL LIBRARIES CONTAINING THEM

Field of the invention

- 5 The present invention refers to heterobicycle derivatives of general formula (I)



wherein:

- R_1 , is chosen in the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; $RR'N-C_{1-8}$ alkyl, $RR'N$ -aryl, RO -aryl, $R(O)C$ -aryl, $RO(O)C$ -aryl, $RR'N(O)C$ -aryl, (P)-W-NR-aryl, (P)-W-O-aryl, (P)-W-C(O)O-aryl, (P)-W-O(O)C-aryl, (P)-W-C(O)RN-aryl, (P)-W-NR(O)C-aryl;
- 10 R_2 , is chosen in the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; amino C_{1-8} alkyl, aminoaryl, C_{1-8} alkyloxyaryl, hydroxyaryl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl, -
- 15 (side chain), -(side chain)-W-(P) or
- R_1 and R_2 taken together are a C_{1-4} alkyl, C_{2-4} alkenyl, cycloalkyl, benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms;
- R_3 , is chosen in the group consisting H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; $RR'NC_{1-8}$ alkyl, $RR'N$ aryl, $RO-C_{1-8}$ alkyl, $RO(O)C-C_{1-8}$ alkyl, $R(O)C-C_{1-8}$ alkyl, $RC(O)O-C_{1-8}$ alkyl, $RC(O)N(R)C_{1-8}$ alkyl RO -aryl, $RO(O)C$ -aryl, $R(O)C$ -aryl $RC(O)O$ -aryl, $RC(O)N(R)$ aryl, -CH(amino acid side-chain) CO_2R , -CH(amino acid side-chain) $C(O)NR$, -CH(amino acid side-chain)- $C(O)O$ -W-(P), -CH(amino acid side-chain)- $C(O)N(R)$ -W-(P), $CH(CO_2R)$ -amino acid side-chain-W-(P), $CH(CONRR')$ -amino acid side-chain-W-(P), protecting group;
- 20 R_4 and R_5 , same or different, are chosen in the group consisting H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl;
- 25

R_6 is chosen in the group consisting, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle, heterocycle C_{1-8} alkyl; $-C(O)R$, $-C(O)OR$, $-C(O)NRR'$, CH_2OR , CH_2NRR' , $-C(O)NH-CH(\text{amino acid side-chain})C(O)OR$, $-C(O)O-W-(P)$, $-C(O)N(R)-W-(P)$, $-CH_2O-W-(P)$, $-CH_2N(R)-W-(P)$;

- 5 R and R', same or different, are chosen in the group consisting of: H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; a protecting group, $-C(O)CH(\text{amino acid side-chain})-NHR$, $-NH-CH(\text{amino acid side-chain})COOR$, $-CH(\text{amino acid side-chain})COOR$;

P is resin, both soluble or bound to a solid support;

- 10 W is as linker;

X is O, S, when a is a double bond, or X is H and a is single bond,

Y and Z, same or different, are O, S, SO, SO_2 , N-R, wherein R is as above defined;

the above said alkyl-, alkenyl-, alkynyl-, cycloalkyl-, aryl- and heterocycle-groups,

- 15 being possibly substituted.

The application refers also to a process for the preparation of the above said compounds, to libraries containing them and to the generation of such combinatorial libraries composed of compounds of formula I, in mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or
20 automated fashion. Compounds of formula I and their libraries are useful to discover new leads for therapeutical applications.

State of the art

The process of discovering new therapeutically active compounds involves the screening of a large number of compounds, in order to develop a structure-activity
25 relationships and select the structures which could represent a new lead for the biological target. Fast methods are necessary to prepare a large collection of compounds to submit to the screening and this, in recent years, can be achieved by preparation of combinatorial chemical libraries of well designed chemical compounds by using immobilization techniques on soluble or insoluble resins.

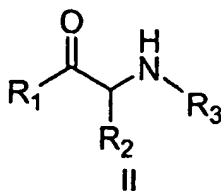
- 30 Heterocycles compounds, bearing different substituents, and functionalised with reactive groups suitable for anchoring on resins, are very useful for this new type

of synthetic strategy (for example see US 5,925,527). Another important point for a well designed chemical library is the complete control of the configuration of the stereogenic centers and the possibility to have enantiopure compounds. All these above mentioned features can be incorporated in compounds of general formula

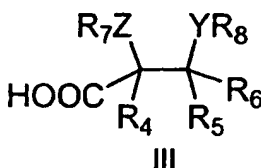
5 (I) which can be obtained with only two reaction steps starting from easily prepared precursors, available also as pure enantiomers. This new type of compounds, having a rigid bicyclic structure, can be functionalised in several positions and allows the easy anchoring on resin support, thus representing a new scaffold for the generation of combinatorial libraries. Thus compounds of general
10 formula (I) can be used for the discover of new leads for therapeutical applications.

Compounds of general formula (I) having $R_1 = H$, Y and Z = O, have been already prepared as it is described by us in *JOC* 1999, 64, 7347 by a process involving various steps starting from a suitable α -amino alcohol which is coupled with a
15 tartaric acid derivative. The prepared intermediate required an oxidation of the primary alcohol function to the corresponding aldehyde and a subsequent trans-acetalization to arrive to compounds I having $R_1 = H$ and X,Y and Z = O. However, it can be seen that the above described process involves many steps which can have a negative effect on the final yields of the desired compounds and the
20 application cannot be extended to compound having R_1 different from H, and Z and Y different from O. Moreover this above described process is limited because, involving also an oxidative step, is compatible only with the functions resistant to the oxidative conditions and requires the protection of the all function sensitive to oxidation.

25 Therefore the application refers to a new straightforward process which, in only two steps, can produce compounds I, where R_1 is different from H, by starting from α -aminoketone II



and acid derivative III,



- 5 commercially available or easily prepared by reported procedures. Moreover, this procedure, allowing the immobilization of each the precursors II or III to a soluble or insoluble resin support, is suitable for the synthesis of combinatorial chemical libraries (see for examples *J Med Chem* **1999**, 42, 3743; US 5,958,792, US 5,302,589) either as separate synthesis, in mixture synthesis,
- 10 split and recombine synthesis, parallel synthesis with manual or automated fashion.

Detailed description of the invention

- The present invention allows to overcome the above said problems thanks to the compounds of formula (I) as above defined useful either as individual compounds
- 15 or for generation of combinatorial chemical libraries either in mixture synthesis or parallel synthesis with manual or automated fashion.

Moreover the invention refers to a new an advantageous process for the preparation of the above defined compounds of formula (I) and their use for discovering new leads for therapeutical applications.

- 20 According to the present invention in the compounds of formula (I) as above defined:

Resin (P) means any polymeric material either soluble in the solvents commonly used in organic synthesis or bound to the solid support;

Solid support is any solid material (at room temperature) to which starting resin materials (reactive groups) may be bound;

W is any molecule which can be used as linker to bound the resin P to the reagents and the products of formula (I);

- 5 Protecting group means any group capable of preventing the atom to which it is attached from participating in an undesired reaction or bonding, as commonly used in synthesis reactions.

Amino acid side-chain means the side chain moieties of the natural occurring L or D amino acids or the non naturally occurring amino acids;

- 10 More preferably the resin is a polymeric material derivatised with a reactive group such as, for example, a $-NH_2$ group or other electron donating group such as an hydroxyl group.

- Preferred solid support materials comprise polymeric compounds such as polyethylene and polystyrene compounds and related inert polymeric compounds. The substrate may be in any shape including sheets, the inside of a cylindrical vessel, or pins but are preferably in the form of spherical beads less than 1.0 cm in diameter more preferably less than 1.0 mm in diameter. A "substrate" or solid support is a conventional solid support material used in peptide synthesis. Non-limiting examples of such substrates or supports include
- 15 a variety of support resins and connectors to the support resins such as those which are photocleavable, DKP-forming linkers (DKP is diketopiperazine; see, e.g., WO90/09395 incorporated herein by reference), TFA cleavable, HF cleavable, fluoride ion cleavable, reductively cleavable and base-labile linkers. A solid support resin comprises a plurality of solid support particles which can
- 20 be split into portions for separate reactions and recombined as desired.

- Preferred protecting groups are those which prevent reaction or bonding of oxygen, nitrogen, carboxylic acids, thiols, alcohols, amines and the like. Such groups and their preparation and introduction are conventional in the art and include, for example, for the reactive function OH: benzyl, *tert*-butyl; acetals, esters, trialkylsilylethers; for COOH group: methyl, *tert*-butyl, benzyl, allyl esters;
- 30 for the NH group: t-Boc, Fmoc, CBz, Bn, Bz.

Amino acid side-chain means the different amino acid side-chain moieties attached to an "amino acid". The term "amino acid" includes any one of the twenty L or D natural α -amino acids having as "side chain": -H of glycine; -CH₃ of alanine; -CH(CH₃)₂ of valine; -CH₂CH(CH₃)₂ of leucine; -CH(CH₃)CH₂CH₃ of isoleucine; -CH₂OH of serine; -CH(OH)CH₃ of threonine; -CH₂SH of cysteine; -CH₂CH₂SCH₃ of methionine; -CH₂-(phenyl) of phenylalanine; -CH₂-(phenyl)-OH of tyrosine; -CH₂-(indole group) of tryptophan; -CH₂COOH of aspartic acid; -CH₂C(O)(NH₂) of asparagine; -CH₂CH₂COOH of glutamic acid; -CH₂CH₂C(O)NH₂ of glutamine; -CH₂CH₂CH₂-N(H)C(NH₂)NH₂ of arginine; -CH₂-(imidazole) group of histidine; and -CH₂(CH₂)₃NH₂ of lysine, comprising the same amino acid side-chain moieties bearing suitable protecting groups (Pg). In addition, the term "amino acid" include also non naturally occurring amino acids, like norleucine (Nle), norvaline (NVa), β -alanine, L or D α -phenyl glycine and others well known in the peptide art.

In the compounds of formula (I), as above defined, groups C₁₋₈ alkyl, C₂₋₈ alkenyl and C₂₋₈ alkynyl represent linear or branched alkyl radicals as for example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propine, butine etc

The term cycloalkyl represents: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane.

The term aryl specifies phenyl, biphenyl and naphthyl groups substituted with one or more, and preferably one or two moieties chosen from the groups consisting of halogen, cyano, nitro, C₁₋₆ alkyl. The term heterocycle represents in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, piperidine.

The term halogen represent fluorine, chlorine, bromine, iodine.

The terms "library", "combinatorial library", "resin-derived library" and the like are used interchangeably throughout the description to mean a series of separate individual components or mixture of the compounds I, synthesized in solution or on a solid support from one or more solid phase bound resin starting materials. and their pharmaceutically acceptable salts or esters.

The synthetic process according to the invention involves only two steps and moreover uses, as starting compounds, an α -aminoketone and a carboxylic acid derivative bearing two vicinal nucleophilic groups like OH, SH, or NHR, preferably belonging to the classes of α,β -dihydroxy acid or α -amino- β -hydroxy acid or α -hydroxy- β -amino acid or α,β -dithiol acid derivatives.

In particular, the process according to the present invention allows the preparation of the compounds of formula (I) wherein:

a = double bond, and X = O or a = single bond and X = H

Y and Z, same or different are O, S, NR wherein R is above described

10 R_1 = methyl, ethyl, propyl, isopropyl, t-butyl, benzyl, phenyl, 4-hydrophenyl, 4-methoxy-phenyl, 4-carboxy-phenyl, 4-nitro-phenyl, 4-amino-phenyl, 4-halogen-phenyl, 4-trifluoromethylphenyl, 2-hydrophenyl, 2-methoxy-phenyl, 2-carboxy-phenyl, 2-nitro-phenyl, 2-amino-phenyl, 2-halogen-phenyl, 2-trifluoromethylphenyl, C_{1-8} alkylOC(O)phenyl, hydroxy- C_{1-8} alkylphenyl, methoxy- C_{1-8} alkylphenyl, 15 $RR'NC(O)$ -phenyl, $RR'N-C_{1-8}$ alkylphenyl, biphenyl, naphthyl, tetrahydronaphthyl, decahydronaphthyl, cycloalkyl, heterocycle, (P)-W-NR-phenyl, (P)-W-O-phenyl, (P)-W-C(O)O-phenyl, (P)-W-O(O)C-phenyl, (P)-W-C(O)RN-phenyl, (P)-W-NR(O)C-phenyl, wherein (P), W, R and R' are defined as above;

R_2 , which can be bound with R_1 through a C_1-C_5 alkyl chain, is chosen in the group 20 consisting of H, methyl, ethyl, propyl, isopropyl, t-butyl, phenyl, 4-hydrophenyl, 4-methoxy-phenyl, 4-carboxy-phenyl, 4-amino-phenyl, benzyl, amino acid side chain-, (P)-W-amino acid side-chain;

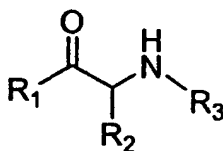
R_3 , H, methyl, ethyl, propyl, isopropyl, t-butyl, phenyl, benzyl, cycloalkyl, aryl, aryl C_{1-8} alkyl; heterocycle, heterocycle C_{1-8} alkyl-CH(amino acid side-chain) CO_2R , 25 CH(amino acid side-chain)C(O)NR, -CH(amino acid side-chain)-C(O)O-W-(P), -CH(amino acid side-chain)-C(O)N(R)-W-(P), CH(CO_2R)-amino acid side-chain-W-(P), CH(CONRR')- amino acid side-chain-W-(P), Pg, wherein (P), (amino acid side-chain), W, R and R' are defined as above;

R_4 , R_5 , same or different, are chosen in the group consisting H, methyl, ethyl, 30 propyl, isopropyl, phenyl, benzyl, heterocycle

R_6 is chosen in the group consisting, H, methyl, ethyl, propyl, isopropyl, t-butyl, phenyl, benzyl, cycloalkyl, aryl, benzyl, heterocycle, heterocycle C_{1-8} alkyl; COOH, COOR, C(O)R, CONHR CONRR', CH_2OH , CH_2OR CH_2NHR , CH_2NRR' , -C(O)NH-CH(amino acid side-chain)C(O)OR, -C(O)O-W-(P), -C(O)N(R)-W-(P), -CH₂O-W-(P), -CH₂N(R)-W-(P), wherein R and R' same or different and the terms "(amino acid side-chain)", "(P)", and "W" are as above defined

Among the pharmaceutically acceptable esters and salts according to the present invention the following can be mentioned: hydrochloride, sulfate, citrate, formate, phosphate.

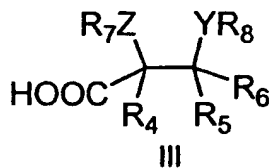
- 10 According to the invention the above defined compounds of formula (I) can be prepared starting from compounds of general formula II



II

wherein R_1 , R_2 , R_3 , are as above defined

- 15 and III



III

wherein R_4 , R_5 , R_6 , Y and Z are as above defined,

and R_7 , R_8 represent H or suitable protecting groups, (Pg) which can be same or different, cyclic or acyclic, and which can be cleaved in acidic conditions.

- 20 The α -amino ketones II are commercially available or can be prepared as shown in the scheme 2, for example starting from an α -halogen-ketone V and a primary amine VI according to known procedures (see for example *Tetrahedron Letters* 1987, 28, 1287 and references cited therein)

The acid derivatives III are commercial available or can be prepared according to known procedures.

As it can be seen from the Scheme 1 the preparation of the compounds (I) according to the invention involves, in the Step 1, the reaction of the α -amino ketone II with the acid derivative III to give the amide derivative IV in the presence of a coupling reagent. Because Step I involves the formation of an amide bond, all the reagents commonly used for the peptide synthesis can be applied to this step. Preferably the reaction is performed in an aprotic polar solvent, preferably CH_2Cl_2 or DMF, at a temperature comprised between 0°C - 100°C , preferably at 25°C , for a time comprised between 1 and 24 hours, preferably in the presence of a coupling agent and activator of the carboxy group, as PyBrOP, PyBOP, HATU, HOBt, HBTU, TBTU, DCC, DIC, EDC etc. and a tertiary base as NEt_3 , DIPEA, NMM. In addition, the activation of the carboxylic acid III, for the condensation reaction with II, can be performed by transformation of the carboxylic group in an anhydride group which smoothly reacts with the amino group of II at room temperature to give the compound IV.

The intermediate amide IV is then cyclized into the final compound I in the Step 2, by action of an acid, which, allows the ketalization of the functions Z and Y with the carbonyl group by also removing the protecting groups Pg, when present. Also for this step the reaction conditions (temperature and time) and the type of acid and solvent are important.

The best results were obtained using a stoichiometric or preferably catalytic amount of a strong acid, preferably sulphuric acid adsorbed on silica gel, p-toluenesulphonic acid, hydrochloride acid, trifluoroacetic acid, trifluoromethanesulphonic acid and performing the reaction at a temperature comprised between 0°C - 150°C , preferably at room temperature or at refluxing-solvent temperature, in an organic apolar solvent (for example methylene chloride, chloroform, benzene or toluene) or in a polar solvent (for example methanol, ethanol) for a time comprised between 15 min and 24 hours, preferably 30 min - 2 hours, preferably with the simultaneous removal of a portion of the solvent and eventually in the presence of molecular sieves. In these conditions the final product I is obtained having $\text{X}=\text{O}$ and

a double bond. The subsequent reaction on the amide bond either with usual reducing agents, for example LiAlH_4 , $\text{BH}_3\cdot\text{THF}$, $\text{BH}_3\cdot\text{Me}_2\text{S}$ and like, produce compounds I wherein $\text{X}=\text{H}$ and a is single bond, or by the use of sulphurating agents, like the Lawesson reagent, produce compounds I wherein $\text{X}=\text{S}$ and a is double bond.

Owing to the importance to produce combinatorial chemical libraries, the above reported procedure can be modified by using one of the two components II and III of the Step 1 bound to a resin through a suitable linker. In this case, the formed compound IV is also bound to a resin, and the following step 2 can be performed either maintaining the final product I bound to the resin or with a simultaneous cleavage from the resin. Because the starting α -amino ketone II can be easily prepared from an α -halogen ketone V and a primary amine VI (as reported in the Scheme 2), this can increase the molecular diversity of compounds II, by starting from one of the two components V or VI, already immobilized on the resin-support.

Specific compounds I prepared according to the process of the invention are reported in the following table:

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1.	O	O	O	Ph	H	PhCH ₂	H	H	COOH
2.	O	O	O	4-HO-Ph	H	PhCH ₂	H	H	COOH
3.	O	O	O	4-O ₂ N-Ph	H	PhCH ₂	H	H	COOH
4.	O	O	O	4-H ₂ N-Ph	H	PhCH ₂	H	H	COOH
5.	O	O	O	4-MeO(O)C-Ph	H	PhCH ₂	H	H	COOH
6.	O	O	O	4-Me-Ph	H	PhCH ₂	H	H	COOH
7.	O	O	O	4-MeO-Ph	H	PhCH ₂	H	H	COOH
8.	O	O	O	4-Cl-Ph	H	PhCH ₂	H	H	COOH
9.	O	O	O	4-Br-Ph	H	PhCH ₂	H	H	COOH
10.	O	O	O	2-HO-Ph	H	PhCH ₂	H	H	COOH
11.	O	O	O	2-O ₂ N-Ph	H	PhCH ₂	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
12.	O	O	O	2-H ₂ N-Ph	H	PhCH ₂	H	H	COOH
13.	O	O	O	2-MeO(O)C-Ph	H	PhCH ₂	H	H	COOH
14.	O	O	O	2-Me-Ph	H	PhCH ₂	H	H	COOH
15.	O	O	O	2-MeO-Ph	H	PhCH ₂	H	H	COOH
16.	O	O	O	2-Cl-Ph	H	PhCH ₂	H	H	COOH
17.	O	O	O	2-Br-Ph	H	PhCH ₂	H	H	COOH
18.	O	O	O	2-Nafthyl	H	PhCH ₂	H	H	COOH
19.	O	O	O	2-thienyl	H	PhCH ₂	H	H	COOH
20.	O	O	O	4-biphenyl	H	PhCH ₂	H	H	COOH
21.	O	O	O	Ph	H	Me	H	H	COOH
22.	O	O	O	Ph	H	CH ₃ (CH ₂) ₂	H	H	COOH
23.	O	O	O	Ph	H	cyclohexyl	H	H	COOH
24.	O	O	O	Ph	H	allyl	H	H	COOH
25.	O	O	O	Ph	H	Ph	H	H	COOH
26.	O	O	O	Ph	H	4-HO-Ph	H	H	COOH
27.	O	O	O	Ph	H	4-O ₂ N-Ph	H	H	COOH
28.	O	O	O	Ph	H	4-MeO ₂ C-Ph	H	H	COOH
29.	O	O	O	Ph	H	4-Me-Ph	H	H	COOH
30.	O	O	O	Ph	H	4-MeO-Ph	H	H	COOH
31.	O	O	O	Ph	H	4-Cl-Ph	H	H	COOH
32.	O	O	O	Ph	H	4-Br-Ph	H	H	COOH
33.	O	O	O	Ph	H	2-HO-Ph	H	H	COOH
34.	O	O	O	Ph	H	2-O ₂ N-Ph	H	H	COOH
35.	O	O	O	Ph	H	2-MeO ₂ C-Ph	H	H	COOH
36.	O	O	O	Ph	H	2-Me-Ph	H	H	COOH
37.	O	O	O	Ph	H	2-MeO-Ph	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
38.	O	O	O	Ph	H	2-Cl-Ph	H	H	COOH
39.	O	O	O	Ph	H	2-Br-Ph	H	H	COOH
40.	O	O	O	Ph	H	2-Naphthyl	H	H	COOH
41.	O	O	O	Ph	H	2-thienyl	H	H	COOH
42.	O	O	O	Ph	H	4-biphenyl	H	H	COOH
43.	O	O	O	Ph	H	4-MeO ₂ C-PhCH ₂	H	H	COOH
44.	O	O	O	Ph	H	4-Me-PhCH ₂	H	H	COOH
45.	O	O	O	Ph	H	4-MeOPhCH ₂	H	H	COOH
46.	O	O	O	Ph	H	4-Cl-PhCH ₂	H	H	COOH
47.	O	O	O	Ph	H	4-Br-PhCH ₂	H	H	COOH
48.	O	O	O	Ph	H	2-HO-PhCH ₂	H	H	COOH
49.	O	O	O	Ph	H	2-O ₂ N-PhCH ₂	H	H	COOH
50.	O	O	O	Ph	H	2-MeO ₂ C-PhCH ₂	H	H	COOH
51.	O	O	O	Ph	H	2-Me-PhCH ₂	H	H	COOH
52.	O	O	O	Ph	H	2-MeO-PhCH ₂	H	H	COOH
53.	O	O	O	Ph	H	2-Cl-PhCH ₂	H	H	COOH
54.	O	O	O	Ph	H	2-Br-PhCH ₂	H	H	COOH
55.	O	O	O	4-HO-Ph	H	4-HO-Ph CH ₂	H	H	COOH
56.	O	O	O	4-HO-Ph	H	4-O ₂ N-PhCH ₂	H	H	COOH
57.	O	O	O	4-HO-Ph	H	4-MeO ₂ C-PhCH ₂	H	H	COOH
58.	O	O	O	4-HO-Ph	H	4-Me-PhCH ₂	H	H	COOH
59.	O	O	O	4-HO-Ph	H	4-MeOPhCH ₂	H	H	COOH
60.	O	O	O	4-HO-Ph	H	4-Cl-PhCH ₂	H	H	COOH
61.	O	O	O	4-HO-Ph	H	4-Br-PhCH ₂	H	H	COOH
62.	O	O	O	4-HO-Ph	H	2-HO-PhCH ₂	H	H	COOH
63.	O	O	O	4-HO-Ph	H	2-O ₂ N-PhCH ₂	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
64.	O	O	O	4-HO-Ph	H	2-MeO ₂ C-PhCH ₂	H	H	COOH
65.	O	O	O	4-HO-Ph	H	2-Me-PhCH ₂	H	H	COOH
66.	O	O	O	4-HO-Ph	H	2-MeO-PhCH ₂	H	H	COOH
67.	O	O	O	4-HO-Ph	H	2-Cl-PhCH ₂	H	H	COOH
68.	O	O	O	4-HO-Ph	H	2-Br-PhCH ₂	H	H	COOH
69.	O	O	O	4-HO-Ph	H	Me	H	H	COOH
70.	O	O	O	4-HO-Ph	H	CH ₃ (CH ₂) ₂	H	H	COOH
71.	O	O	O	4-HO-Ph	H	cyclohexyl	H	H	COOH
72.	O	O	O	4-HO-Ph	H	allyl	H	H	COOH
73.	O	O	O	Ph	H	HO ₂ C-CH ₂	H	H	COOH
74.	O	O	O	Ph	H	Bn(HO ₂ C)CH	H	H	COOH
75.	O	O	O	Ph	H	HOCH ₂ (HO ₂ C)CH	H	H	COOH
76.	O	O	O	Ph	H	CH ₃ (HO)CH(HO ₂ C)CH	H	H	COOH
77.	O	O	O	Ph	H	MeS(CH ₂) ₂ (HO ₂ C)CH	H	H	COOH
78.	O	O	O	Ph	H	H ₂ N(CH ₂) ₃ (HO ₂ C)CH	H	H	COOH
79.	O	O	O	Ph	H	HO ₂ CCH ₂ (HO ₂ C)CH	H	H	COOH
80.	O	O	O	Ph	H	imidazole-CH ₂ (HO ₂ C)CH	H	H	COOH
81.	O	O	O	Ph	H	indole-CH ₂ (HO ₂ C)CH	H	H	COOH
82.	O	O	O	4-HO-Ph	H	HO ₂ C-CH ₂	H	H	COOH
83.	O	O	O	4-HO-Ph	H	Me(HO ₂ C)CH	H	H	COOH
84.	O	O	O	4-HO-Ph	H	(CH ₃) ₂ CH(HO ₂ C)CH	H	H	COOH
85.	O	O	O	4-HO-Ph	H	Bn(HO ₂ C)CH	H	H	COOH
86.	O	O	O	4-HO-Ph	H	HOCH ₂ (HO ₂ C)CH	H	H	COOH
87.	O	O	O	4-HO-Ph	H	CH ₃ (HO)CH(HO ₂ C)CH	H	H	COOH
88.	O	O	O	4-HO-Ph	H	MeS(CH ₂) ₂ (HO ₂ C)CH	H	H	COOH
89.	O	O	O	4-HO-Ph	H	H ₂ N(CH ₂) ₃ (HO ₂ C)CH	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
90.	O	O	O	4-HO-Ph	H	HO ₂ CCH ₂ (HO ₂ C)CH	H	H	COOH
91.	O	O	O	4-HO-Ph	H	imidazole-CH ₂ (HO ₂ C)CH	H	H	COOH
92.	O	O	O	4-HO-Ph	H	indole-CH ₂ (HO ₂ C)CH	H	H	COOH
93.	O	O	O	Ph	Me	PhCH ₂	H	H	COOH
94.	O	O	O	4-HO-Ph	Me	PhCH ₂	H	H	COOH
95.	O	O	O	Ph	Bn	PhCH ₂	H	H	COOH
96.	O	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	COOH
97.	O	O	O	Ph	Me	HO ₂ C-CH ₂	H	H	COOH
98.	O	O	O	4-HO-Ph	Me	HO ₂ C-CH ₂	H	H	COOH
99.	O	O	O	Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
100.	O	O	O	4-HO-Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
101.	O	O	O	Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
102.	O	O	O	4-HO-Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
103.	O	HN	O	Ph	H	PhCH ₂	H	H	CH ₃
104.	O	HN	O	Ph	Me	PhCH ₂	H	H	CH ₃
105.	O	HN	O	Ph	Bn	PhCH ₂	H	H	CH ₃
106.	O	HN	O	4-OH-Ph	H	PhCH ₂	H	H	CH ₃
107.	O	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	CH ₃
108.	O	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	CH ₃
109.	O	HN	O	Ph	H	Ph	H	H	CH ₃
110.	O	HN	O	Ph	Me	Ph	H	H	CH ₃
111.	O	HN	O	Ph	Bn	Ph	H	H	CH ₃
112.	O	HN	O	4-OH-Ph	H	Ph	H	H	CH ₃
113.	O	HN	O	4-OH-Ph	Me	Ph	H	H	CH ₃
114.	O	HN	O	4-OH-Ph	Bn	Ph	H	H	CH ₃
115.	O	HN	O	Ph	H	CH ₃ -Ph	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
116.	O	HN	O	Ph	Me	CH ₃ -Ph	H	H	CH ₃
117.	O	HN	O	Ph	Bn	CH ₃ -Ph	H	H	CH ₃
118.	O	HN	O	4-OH-Ph	H	CH ₃ -Ph	H	H	CH ₃
119.	O	HN	O	4-OH-Ph	Me	CH ₃ -Ph	H	H	CH ₃
120.	O	HN	O	4-OH-Ph	Bn	CH ₃ -Ph	H	H	CH ₃
121.	O	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
122.	O	HN	O	Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
123.	O	HN	O	Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
124.	O	HN	O	4-OH-Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
125.	O	HN	O	4-OH-Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
126.	O	HN	O	4-OH-Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
127.	O	HN	O	Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
128.	O	HN	O	Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
129.	O	HN	O	Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
130.	O	HN	O	4-OH-Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
131.	O	HN	O	4-OH-Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
132.	O	HN	O	4-OH-Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
133.	O	HN	O	Ph	H	Me	H	H	CH ₃
134.	O	HN	O	Ph	H	CH ₃ (CH ₂) ₂	H	H	CH ₃
135.	O	HN	O	Ph	H	cyclohexyl	H	H	CH ₃
136.	O	HN	O	Ph	H	allyl	H	H	CH ₃
137.	O	HN	O	4-OH-Ph	H	Me	H	H	CH ₃
138.	O	HN	O	4-OH-Ph	H	CH ₃ (CH ₂) ₂	H	H	CH ₃
139.	O	HN	O	4-OH-Ph	H	cyclohexyl	H	H	CH ₃
140.	O	HN	O	4-OH-Ph	H	allyl	H	H	CH ₃
141.	O	HN	O	Ph	H	HO ₂ C-CH ₂	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
142.	O	HN	O	Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
143.	O	HN	O	Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
144.	O	HN	O	4-OH-Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
145.	O	HN	O	4-OH-Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
146.	O	HN	O	4-OH-Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
147.	O	HN	O	Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
148.	O	HN	O	Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
149.	O	HN	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
150.	O	HN	O	4-OH-Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
151.	O	HN	O	4-OH-Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
152.	O	HN	O	4-OH-Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
153.	H	O	O	Ph	H	PhCH ₂	H	H	COOH
154.	H	O	O	Ph	Me	PhCH ₂	H	H	COOH
155.	H	O	O	Ph	Bn	PhCH ₂	H	H	COOH
156.	H	O	O	4-HO-Ph	H	PhCH ₂	H	H	COOH
157.	H	O	O	4-HO-Ph	Me	PhCH ₂	H	H	COOH
158.	H	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	COOH
159.	H	O	O	Ph	H	HO ₂ C-CH ₂	H	H	COOH
160.	H	O	O	Ph	Me	HO ₂ C-CH ₂	H	H	COOH
161.	H	O	O	Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
162.	H	O	O	4-HO-Ph	H	HO ₂ C-CH ₂	H	H	COOH
163.	H	O	O	4-HO-Ph	Me	HO ₂ C-CH ₂	H	H	COOH
164.	H	O	O	4-HO-Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
165.	H	O	O	Ph	H	Bn(HO ₂ C)CH	H	H	COOH
166.	H	O	O	Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
167.	H	O	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
168.	H	O	O	4-HO-Ph	H	Bn(HO ₂ C)CH	H	H	COOH
169.	H	O	O	4-HO-Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
170.	H	O	O	4-HO-Ph	Bn	Bn(HO ₂ C)CH	H	H	COOH
171.	H	HN	O	Ph	H	PhCH ₂	H	H	CH ₃
172.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
173.	H	HN	O	Ph	Me	PhCH ₂	H	H	CH ₃
174.	H	HN	O	Ph	Bn	PhCH ₂	H	H	CH ₃
175.	H	HN	O	4-OH-Ph	H	PhCH ₂	H	H	CH ₃
176.	H	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	CH ₃
177.	H	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	CH ₃
178.	H	HN	O	Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
179.	H	HN	O	Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
180.	H	HN	O	Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
181.	H	HN	O	4-OH-Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
182.	H	HN	O	4-OH-Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
183.	H	HN	O	4-OH-Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
184.	H	HN	O	Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
185.	H	HN	O	Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
186.	H	HN	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
187.	H	HN	O	4-OH-Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
188.	H	HN	O	4-OH-Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
189.	H	HN	O	4-OH-Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
190.	H	HN	O	Ph	H	Ph	H	H	CH ₃
191.	H	HN	O	Ph	Me	Ph	H	H	CH ₃
192.	H	HN	O	Ph	Bn	Ph	H	H	CH ₃
193.	H	HN	O	4-OH-Ph	H	Ph	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
194.	H	HN	O	4-OH-Ph	Me	Ph	H	H	CH ₃
195.	H	HN	O	4-OH-Ph	Bn	Ph	H	H	CH ₃
196.	H	HN	O	Ph	H	CH ₃ -Ph	H	H	CH ₃
197.	H	HN	O	Ph	Me	CH ₃ -Ph	H	H	CH ₃
198.	H	HN	O	Ph	Bn	CH ₃ -Ph	H	H	CH ₃
199.	H	HN	O	4-OH-Ph	H	CH ₃ -Ph	H	H	CH ₃
200.	H	HN	O	4-OH-Ph	Me	CH ₃ -Ph	H	H	CH ₃
201.	H	HN	O	4-OH-Ph	Bn	CH ₃ -Ph	H	H	CH ₃
202.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
203.	H	HN	O	Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
204.	H	HN	O	Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
205.	H	HN	O	4-OH-Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
206.	H	HN	O	4-OH-Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
207.	H	HN	O	4-OH-Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
208.	H	HN	O	Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
209.	H	HN	O	Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
210.	H	HN	O	Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
211.	H	HN	O	4-OH-Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
212.	H	HN	O	4-OH-Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
213.	H	HN	O	4-OH-Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
214.	H	O	O	Ph	H	PhCH ₂	H	H	CH ₂ OH
215.	H	O	O	Ph	H	4-MeOPhCH ₂	H	H	CH ₂ OH
216.	H	O	O	Ph	Me	PhCH ₂	H	H	CH ₂ OH
217.	H	O	O	Ph	Bn	PhCH ₂	H	H	CH ₂ OH
218.	H	O	O	4-HO-Ph	H	PhCH ₂	H	H	CH ₂ OH
219.	H	O	O	4-HO-Ph	Me	PhCH ₂	H	H	CH ₂ OH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
220.	H	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	CH ₂ OH
221.	H	O	O	Ph	H	HOCH ₂	H	H	CH ₂ OH
222.	H	O	O	Ph	Me	HOCH ₂	H	H	CH ₂ OH
223.	H	O	O	Ph	Bn	HOCH ₂	H	H	CH ₂ OH
224.	H	O	O	4-HO-Ph	H	HOCH ₂	H	H	CH ₂ OH
225.	H	O	O	4-HO-Ph	Me	HOCH ₂	H	H	CH ₂ OH
226.	H	O	O	4-HO-Ph	Bn	HOCH ₂	H	H	CH ₂ OH
227.	H	O	O	Ph	H	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
228.	H	O	O	Ph	Me	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
229.	H	O	O	Ph	Bn	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
230.	H	O	O	4-HO-Ph	H	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
231.	H	O	O	4-HO-Ph	Me	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
232.	H	O	O	4-HO-Ph	Bn	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
233.	H	HN	O	Ph	H	PhCH ₂	H	H	H
234.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	H
235.	H	HN	O	Ph	Me	PhCH ₂	H	H	H
236.	H	HN	O	Ph	Bn	PhCH ₂	H	H	H
237.	H	HN	O	4-OH-Ph	H	PhCH ₂	H	H	H
238.	H	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	H
239.	H	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	H
240.	H	HN	O	Ph	H	HOCH ₂	H	H	H
241.	H	HN	O	Ph	Me	HOCH ₂	H	H	H
242.	H	HN	O	Ph	Bn	HOCH ₂	H	H	H
243.	H	HN	O	4-OH-Ph	H	HOCH ₂	H	H	H
244.	H	HN	O	4-OH-Ph	Me	HOCH ₂	H	H	H
245.	H	HN	O	4-OH-Ph	Bn	HOCH ₂	H	H	H

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
246.	H	HN	O	Ph	H	Bn(HOH ₂ C)CH	H	H	H
247.	H	HN	O	Ph	Me	Bn(HOH ₂ C)CH	H	H	H
248.	H	HN	O	Ph	Bn	Bn(HOH ₂ C)CH	H	H	H
249.	H	HN	O	4-OH-Ph	H	Bn(HOH ₂ C)CH	H	H	H
250.	H	HN	O	4-OH-Ph	Me	Bn(HOH ₂ C)CH	H	H	H
251.	H	HN	S	Ph	H	PhCH ₂	H	H	H
252.	H	HN	S	Ph	H	4-MeO-PhCH ₂	H	H	H
253.	H	HN	S	Ph	Me	PhCH ₂	H	H	H
254.	H	HN	S	Ph	Bn	PhCH ₂	H	H	H
255.	H	HN	S	4-OH-Ph	H	PhCH ₂	H	H	H
256.	H	HN	S	4-OH-Ph	Me	PhCH ₂	H	H	H
257.	H	HN	S	4-OH-Ph	Bn	PhCH ₂	H	H	H
258.	H	HN	S	Ph	H	HOCH ₂	H	H	H
259.	H	HN	S	Ph	Me	HOCH ₂	H	H	H
260.	H	HN	S	Ph	Bn	HOCH ₂	H	H	H
261.	H	HN	S	4-OH-Ph	H	HOCH ₂	H	H	H
262.	H	HN	S	4-OH-Ph	Me	HOCH ₂	H	H	H
263.	H	HN	S	4-OH-Ph	Bn	HOCH ₂	H	H	H
264.	H	HN	S	Ph	H	Bn(HOH ₂ C)CH	H	H	H
265.	H	HN	S	Ph	Me	Bn(HOH ₂ C)CH	H	H	H
266.	H	HN	S	Ph	Bn	Bn(HOH ₂ C)CH	H	H	H
267.	H	HN	S	4-OH-Ph	H	Bn(HOH ₂ C)CH	H	H	H
268.	H	HN	S	4-OH-Ph	Me	Bn(HOH ₂ C)CH	H	H	H

The invention will be better understood in the light of the following Examples.

EXAMPLE 1

Preparation of *N*-benzyl-*N'*-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7-R_8 = \text{CH}_2-\text{CH}_2$]

To a solution of II (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$) (1.2 g, 5.33 mmol) in anhydrous CH_2Cl_2 (10 ml) (CH_2Cl_2 was filtered through a short pad of anhydrous Na_2CO_3 just before being used) were added, under a nitrogen atmosphere, III (wherein $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7-R_8 = \text{CH}_2-\text{CH}_2$) (1.088 g, 5.33 mmol), PyBrOP (2.49 g, 5.33 mmol), and DIPEA (2.73 mL, 15.99 mmol). The mixture was stirred at room temperature for 2 h, and then the solvent was removed to give an oil that was dissolved in EtOAc. This solution was washed with aqueous 5% KHSO_4 , 5% NaHCO_3 , and brine and dried over Na_2SO_4 . After evaporation of the solvent, the crude product obtained was purified by chromatography (EtOAc-petroleum ether, 1:3, R_f 0.32), yielding IV (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7-R_8 = \text{CH}_2-\text{CH}_2$) (1.645 g, 75%) as a colorless oil:

^1H NMR (CDCl_3): 7.90-7.85 (m, 2H), 7.61-7.22 (m, 8H), 5.39 (d, $J = 5.1\text{Hz}$, 1H), 5.11 (d, $J = 5.1\text{Hz}$, 1 H), 4.88-4.10 (m, 4H), 3.80 (s, 3 H), 1.49 (s, 3 H), 1.31 (s, 3 H).

EXAMPLE 2

Preparation of Methyl (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-5-phenyl-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate [compound I wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$]

A solution of IV (prepared according the example 1, wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7-R_8 = \text{CH}_2-\text{CH}_2$) (1.645 g, 4.00 mmol) in toluene (40 mL) was quickly added to a refluxing suspension of $\text{H}_2\text{SO}_4/\text{SiO}_2$ (30% w/w, 700 mg) in toluene (60 mL). The mixture was allowed to react for 15 min, and afterward, one-third of the solvent was distilled off. The hot reaction mixture was filtered through a short layer of NaHCO_3 , and the solvent evaporated. Alternatively, compound IV was treated in methylene chloride with an

equal volume of trifluoroacetic acid (TFA) and water in a 95:5 TFA/water ratio at room temperature for 30 min.

After evaporation of the solvent, the crude product was purified by chromatography as above affording pure I (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{PhCH}_2$,

5 $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$) (1.200 g, 85%): mp 112 -114 °C;

$[\alpha]_D^{25} - 64.3$ (c 0.8, CDCl_3);

^1H NMR (CDCl_3) 7.62-7.59 (m, 2H), 7.41-7.24 (m, 8H), 5.16 (s, 1H), 4.92 (s, 1H), 4.61 (AB system, $J = 11.0$ Hz, 2H), 3.74 (s, 3 H), 3.46 (AB system, $J =$

10 25.2 Hz, 2H).

^{13}C NMR (CDCl_3); 169.0 (s), 165.4(s), 137.8 (s), 135.0 (s), 129.5 (d), 128.8 (d), 128.3 (d), 127.9, 127.8 (d), 125.4 (d), 107.7 (s), 79.1 (d), 78.3 (d), 55.5 (t), 52.6 (q), 48.6 (t)

IR (CDCl_3): 1762, 1678 cm^{-1}

15 MS (m/z , %): 353 (M^+ , 3), 147 (5), 120(36), 306 (13), 105 (80), 91 (100).

EXAMPLE 3

Preparation of *N*-(*p*-Methoxybenzyl)-*N'*-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV, wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = 4\text{-MeO-C}_6\text{H}_4\text{CH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7\text{---}R_8 = \text{CH}_2\text{---}$

20 CH_2]

A solution of II (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = 4\text{-MeO-C}_6\text{H}_4\text{CH}_2$) (0.5 g, 2.09 mmol) in anhydrous CH_2Cl_2 (5 ml), III (wherein $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7\text{---}R_8 = \text{CH}_2\text{---CH}_2$) (0.427 g, 2.09 mmol), PyBrOP (0.976 g, 2.09 mmol), and DIPEA (1.07 mL, 6.27 mmol) was treated as in the example 1. The crude product

25 obtained was purified by chromatography (EtOAc-petroleum ether, 1:3, R_f 0.32), yielding IV (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = 4\text{-MeO-C}_6\text{H}_4\text{CH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7\text{---}R_8 = \text{CH}_2\text{---CH}_2$) (0.370 g, 40%) as a colorless oil:

^1H NMR (CDCl_3): 7.90-7.85 (m, 2H), 7.61-7.43 (m, 3H), 7.21-7.15 (m, 2H), 6.90-6.82 (m, 2H), 5.39 (d, $J = 5.1\text{Hz}$, 1H), 5.13 (d, $J = 5.1\text{Hz}$, 1 H), 4.75 (m, 2H),

30 4.11 (m, 2H), 3.82 (s, 3 H), 3.79 (s, 3 H), 1.52 (s, 3 H), 1.36 (s, 3 H).

EXAMPLE 4

Preparation of Methyl (1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-5-phenyl-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate [compound I wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O]

- 5 A solution of IV (wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOMe, Z = O, Y = O, R₇-R₈ = CH₂-CH₂) (0.370 g, 0.84 mmol) in toluene (10 mL) or in methylene chloride was treated as reported in example 2. The crude product was purified by chromatography as above affording pure I (wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O) (0.177 g, 55 %): mp 134 - 136 °C;

[α]_D²⁵ - 62.3 (c 0.6, CDCl₃);

¹H NMR (CDCl₃) 7.62-7.59 (m, 2H), 7.41-7.24 (m, 5H), 7.11-6.91 (m, 2H), 5.14 (s, 1H), 4.89 (s, 1H), 4.24 (AB system, *J* = 11.0 Hz, 2H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.56 (AB system, *J* = 23.4 Hz, 2H).

- 15 ¹³C NMR (CDCl₃); 169.4 (s), 165.3(s), 159.8 (s), 137.8 (s), 135.0 (s), 129.5 (d), 128.1 (d), 127.1 (d), 126.4 (d), 119.2 (d), 107.1 (s), 79.8 (d), 78.0 (d), 58.5 (t), 55.1 (q), 52.6 (q), 48.1 (t).

IR (CDCl₃): 1768, 1682 cm⁻¹

MS (*m/z*, %): 383 (M⁺, 5), 121 (100).

20 **EXAMPLE 5**

Preparation of Methyl (1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-5-phenyl-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate [compound I wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O]. As an alternative to the procedure reported in EXAMPLE 4 this

- 25 compound can be prepared reacting 2,3-di-*O*-acetyl tartaric anhydride (351 mg, 1.62 mmol) with II (wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂) (415 mg, 1.62 mmol) in anhydrous CH₂Cl₂ (20 mL) at room temperature. After stirring for 20hrs the solvent was evaporated obtaining crude IV (wherein R₁ = Ph, R₂ = H, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOH, Z = O, Y = O, R₇ = CH₃CO, R₈ = CH₃CO) as an orange solid compounds. This was dissolved in
- 30 MeOH (10 mL) and treated under stirring with SOCl₂ (0.1 mL, 1.37 mmol). The

solution was refluxed for 2hrs, then cooled and evaporated obtaining a crude oil which was dissolved in toluene (15 mL). The flask was poured in an oil bath heated at 90 °C and suspension of H₂SO₄/SiO₂ (30% w/w, 200 mg) was added. The resulting suspension was refluxed for 15 min, then 5 mL of toluene were
5 distilled off. After cooling to room temperature, the reaction mixture was filtered over a short pad of NaHCO₃, washing with EtOAc, evaporated and chromatographed as above obtaining pure I (wherein R₁ = Ph, R₂ = O, R₃ = 4-MeO-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O) (410 mg, 66% overall yield). Spectroscopic and analytical data are identical to those
10 reported for compound I in EXAMPLE 4.

EXAMPLE 6

Preparation of (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-5-(4-hydroxyphenyl)-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid [compound I wherein R₁ = 4-OH-C₆H₄, R₂ = H, R₃ = PhCH₂, R₄ = H, R₅ = H, R₆ = COOH, X = O, Z = O, Y = O]

- 15 Wang resin or hydroxymethylpolystyrene resin (1 g, 200-400 mesh, substitution 0.64 mmol/g) was suspended in CH₂Cl₂ (10 mL) and magnetically stirred for 15 min. After filtration, a solution of Ph₃P (1.024g, 3.904 mmol) and 4'-hydroxy-2-chloroacetophenone (compound V wherein Hal = Cl, R₁ = 4-OH-C₆H₄, R₂ = H), (0.568 g, 3.33 mmol) in a mixture of CH₂Cl₂ (10 mL) and Et₂O (4 mL) was added to
20 the expanded resin. After 5 min, DEAD (607 mL, 3.904 mmol) was added drop-wise and the resulting suspension stirred at room temperature. After 24 h the suspension was filtered and the resin washed with DMF (3 x 10 mL), CH₂Cl₂ (3 x 10 mL), MeOH (3 x 10 mL) and again DMF (3 x 10 mL). Alternatively, Wang resin or hydroxymethylpolystyrene resin (1 g, 200-400 mesh, substitution 0.64 mmol/g)
25 was suspended in anhydrous CH₂Cl₂ (10 mL) under nitrogen atmosphere and Cl₃CCN (1.5 mL) was added. After cooling to 0 °C, DBU (0.1 mL) was added drop-wise in 5 min. After shaking at 0 °C for 40 min the resin was washed with CH₂Cl₂, DMSO, THF, CH₂Cl₂, and finally dried under vacuum. The resin was washed with anhydrous THF under nitrogen atmosphere and then suspended in anhydrous
30 cyclohexane (10 mL). Then a solution of 4'-hydroxy-2-chloroacetophenone (compound V wherein Hal = Cl, R₁ = 4-OH-C₆H₄, R₂ = H) in CH₂Cl₂ (10 mL) and

THF (5 mL) was added. Then $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (50 μL) was added and left under shaking for 20 min. After filtering, the resin was washed with THF, CH_2Cl_2 , and dried under vacuum.

Then, the resin (1.00 g), suspended in CH_2Cl_2 (1 mL), was treated with
5 benzylamine (compound VI wherein $\text{R}_3 = \text{PhCH}_2$) (10 mL) and left under stirring at room temperature for 12 h. After filtration, the resin II ($\text{R}_1 = \text{Wang-4-OH-C}_6\text{H}_4$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{PhCH}_2$) obtained was washed as above with DMF, CH_2Cl_2 , MeOH and again DMF. Resin II ($\text{R}_1 = \text{Wang-4-OH-C}_6\text{H}_4$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{PhCH}_2$) was then coupled with III [wherein $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOMe}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$, $\text{R}_7\text{---R}_8 = \text{CH}_2\text{---CH}_2$]
10 as follows: compound III (261 mg, 1.28 mmol) and PyBroP (597 mg, 1.28 mmol) were added to resin II (500 mg) suspended in DMF (10 mL), then DIPEA (438 μL , 1.28 mmol) was added slowly at room temperature and the resulting suspension stirred for 12 h. After the usual work-up, resin IV [$\text{R}_1 = \text{Wang-4-OH-C}_6\text{H}_4$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{PhCH}_2$, $\text{R}_4 = \text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOMe}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$, $\text{R}_7\text{---R}_8 = \text{CH}_2\text{---CH}_2$]
15 CH_2] was obtained. The cyclization step was performed on 250 mg of resin IV as follows: resin IV (250 mg) and *p*-TsOH (6 mg) were suspended in toluene and the mixture refluxed for 15 min. Then part of the solvent (25 mL) was distilled off and the residual suspension filtered. Alternatively, resin IV was treated in methylene chloride with an equal volume of trifluoroacetic acid (TFA) and water in a 95:5
20 TFA/water ratio at room temperature for 30 min.

After filtration the solution was concentrated obtaining, as a yellow oil, compound I [wherein $\text{R}_1 = 4\text{-OH-C}_6\text{H}_4$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{PhCH}_2$, $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOH}$, $\text{X} = \text{O}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$] (33 mg). with complete cleavage from the resin.

¹H NMR (CDCl₃) δ: 7.78 (d, *J* = 8.8 Hz, 2 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.40-7.00 (m, 3 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.13 (s, 1 H), 4.86 (s, 1 H), 4.58 (AB system, *J* = 15.0 Hz, 2 H), 3.57 (d, *J* = 11.8 Hz, 1 H), 3.38 (d, *J* = 11.8 Hz, 1 H).

EXAMPLE 7

- 5 Preparation of *N*-(4-methylphenyl)-*N'*-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV wherein R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄, R₄=H, R₅= H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂]
To a solution of III (wherein R₄=H, R₅=H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂) (366 mg, 1.8 mmol) in methylene chloride (1.8 ml) and PyBrop (839 mg,
10 1.8 mmol) was added II (wherein R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄) (406mg, 1.8 mmol) and DIPEA (0.765 mL, 3.6 mmol). The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (AcOEt- Petroleum Ether. 1:2, R_f = 0.37) to give IV (R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄, R₄=R₅= H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂) as yellow oil
15 (440 mg, 62%).
¹H NMR δ 8.00-7.90 (m, 2H), 7.62-7.39 (m, 4H), 7.36-7.12 (m, 3H), 5.26 (*J*=17.2 Hz part A of AB system, 1H) 4.96 (*J*=17.2 Hz part B of AB system, 1H), 5.07 (*J*=6.6 Hz part A of AB system, 1H) 4.66 (*J*=6.6 Hz part B of AB system, 1H), 3.74 (s, 3H), 2.36 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H). MS (*m/z*, %): 411 (M⁺, 4), 352 (6),
20 306 (13), 120(100).

EXAMPLE 8

- Preparation of Methyl (1*R*,5*S*,7*R*)-3-(4'-methylphenyl)-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate [compound I wherein R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O]
25 A solution of IV (prepared in the example 7, wherein R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄, R₄=H, R₅= H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂) (310 mg, 0.75 mmol) in toluene (32 ml) was quickly added to a refluxing solution of H₂SO₄/SiO₂ (175 mg) in toluene (16 ml). Alternatively, compound IV was treated in methylene chloride with an equal volume of trifluoroacetic acid (TFA) and water in a 95:5
30 TFA/water ratio at room temperature for 30 min. The mixture was treated as reported in Example 2. The product I [wherein R₁ = Ph, R₂ = H, R₃ = 4-Me-C₆H₄, R₄

= H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O] was obtained in pure form (260 mg, 97%).

¹H NMR δ: 7.78-7.66 (m, 2H), 7.48-7.36 (m, 4H), 7.30-7.10 (m, 3H), 5.23 (s, 1H), 5.02 (s, 1H), 4.02 (J=12 Hz part A of AB system, 1H) 3.90 (J=12 Hz part B of AB system, 1H), 3.73 (s, 3H), 2.35 (s, 3H). ¹³C NMR δ: 168.9(s), 165.1(s), 137.4 (s), 136.8 (s), 135.1(s), 129.9 (d), 129.6 (d), 128.4 (d), 125.4 (d), 125.3(d), 107.6 (s), 79.4 (d), 78.4 (d), 59.2 (t), 52.7 (q), 20.9 (q). MS (m/z, %): 353 (M⁺, 4), 294 (2), 119 (100).

EXAMPLE 9

10 Preparation of *N*-[(1*S*)-(1-carbomethoxy-2-phenylethyl)]-*N'*-[2-oxo-2-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester [compound IV wherein R₁ = Ph, R₂ = H, R₃ = CH(COOMe)CH₂Ph, R₄=H, R₅= H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂].

To a solution of III (wherein R₄=H, R₅=H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂) (118 mg, 0.58 mmol) in CH₂Cl₂ (0.5 mL), and PyBrOP (270 mg, 0.58 mmol) was added II (wherein R₁ = Ph, R₂ = H, R₃ = CH(COOMe)CH₂Ph) (120 mg, 0.4 mmol) and DIPEA (0.255 mL, 1.2 mmol). The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (CH₂Cl₂ - MeOH (40:1) to afford IV (wherein R₁ = Ph, R₂ = H, R₃ = CH(COOMe)CH₂Ph, R₄=H, R₅= H, R₆ = COOMe, Z = O, Y = O, R₇—R₈ = CH₂-CH₂) (160mg, 82%).

The ¹H and ¹³C NMR spectrums show two set of signals in 2:1 ratio. ¹H NMR (CDCl₃) δ: 8.04-7.90 (m, 2H), 7.70-7.42 (m, 4H), 7.38-7.20 (m, 4H), 5.48-4.74 (m, 5H), 3.76 and 3.75 (s, 3H), 3.59 (s, 3H), 3.38-3.30 (m, 2H), 1.56 and 1.46, 1.33, 1.28 (s, 6H). ¹³C NMR (CDCl₃) δ: 193.6, 192.3, 170.7, 170.6, 169.9, 169.4, 168.5, 136.6, 135.9, 135.0, 134.5, 133.7, 129.1, 129.0, 128.7, 128.5, 128.4, 128.3, 127.8, 127.6, 126.8, 126.6, 113.2, 77.2, 76.9, 75.4, 60.3, 59.3, 52.5, 52.3, 51.7, 49.2, 36.4, 35.6, 26.5, 26.3, 26.2, 25.9. MS m/z (%): 483 (M⁺, 2), 424 (4), 378 (7), 320 (16), 206 (34), 192 (50), 162 (63), 105 (100)

30 EXAMPLE 10

Preparation of Methyl (1*R*,5*S*,7*R*)-3-[(1*S*)-1-carbomethoxy-2-phenylethyl]-2-oxo-5-phenyl-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate

[compound I wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOMe})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$]

- 5 A solution of IV (prepared according the example 9, wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOMe})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $Z = \text{O}$, $Y = \text{O}$, $R_7-R_8 = \text{CH}_2-\text{CH}_2$) (150 mg, 0.30 mmol) in toluene (5 ml) was quickly added to a refluxing solution of $\text{H}_2\text{SO}_4/\text{SiO}_2$ (60 mg) in toluene (33 ml). Alternatively, compound IV was treated in methylene chloride with an equal volume of trifluoroacetic acid (TFA) and water in
- 10 a 95:5 TFA/water ratio at room temperature for 30 min. The mixture was treated as reported in Example 2. The crude product was purified by flash chromatography (AcOEt-Petroleum Ether 1:1, $R_f = 0.41$) to afford I (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOMe})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$) as 2:1 mixture of epimers (82 mg, 65%).
- 15 ^1H NMR (CDCl_3) major epimer: δ 7.60 (m, 2 H), 7.90-7.30 (m, 8 H), 5.11 (dd, $J = 5.6, 10.8$ Hz, 1 H), 4.99 (s, 1 H), 4.84 (s, 1 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.75-3.34 (m, 3 H), 3.08 (m, 1 H).
- MS m/z (%): 425 (M^+ , 2), 366 (19), 306 (7), 192 (32), 105 (100), 91 (88), 77 (62).

EXAMPLE 11

- 20 Preparation of N-Boc *N*-(4-methoxybenzyl)-*N'*-[2-oxo-2-phenylethyl]-threoninamide IV (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = p\text{-CH}_3\text{O-C}_6\text{H}_4\text{CH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{Me}$, $R_7 = \text{Boc}$, $R_8 = \text{H}$, $Z = \text{N}$, $Y = \text{O}$).
- To a solution of III ($R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{Me}$, $R_7 = \text{Boc}$, $R_8 = \text{H}$, $Z = \text{N}$, $Y = \text{O}$) in CH_2Cl_2 (5 mL) and PyBrOP (531 mg, 1.14 mmol) was added II (wherein $R_1 =$
- 25 Ph , $R_2 = \text{H}$, $R_3 = p\text{-CH}_3\text{O-C}_6\text{H}_4\text{CH}_2$) (333 mg, 1.14 mmol) and DIPEA (0.585 mL, 3.42 mmol). The mixture The mixture was treated as reported in Example 1. The crude product was purified by column chromatography on silica gel (EtOAc-petrolrum ether, 1:1.5, $R_f = 0.23$) to afford IV (wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = p\text{-CH}_3\text{O-C}_6\text{H}_4\text{CH}_2$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{Me}$, $R_7 = \text{Boc}$, $R_8 = \text{H}$, $Z = \text{N}$, $Y = \text{O}$)
- 30 (232 mg, 44%) as an oil.

¹H NMR (CDCl₃) (1:1 mixture of rotamers) δ 7.85 (d, *J* = 7.3 Hz, 2 H), 7.55 (m, 1 H), 7.42 (m, 2 H), 7.11 (m, 2 H), 6.82 (m, 2 H), 5.50 (m, 1 H), 5.29 (d, *J* = 14.3 Hz, 1 H), 5.00-4.20 (m, 5 H), 4.00 (m, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 1.38 (s, 9 H), 1.31 (s, 9 H), 1.19 (d, *J* = 6.2 Hz, 3 H), 1.07 (d, *J* = 6.2 Hz, 3 H).

5 EXAMPLE 12

Preparation of (1*S*,5*R*,7*R*)-3-(4-methoxybenzyl)-2-oxo-5-phenyl-7-*exo*-methyl-6-oxa-3,8-diazabicyclo[3.2.1]octane [compound I wherein R₁ = Ph, R₂ = H, R₃ = *p*-CH₃O-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = Me, X = O, Z = N, Y = O]

A solution of IV (wherein R₁ = Ph, R₂ = H, R₃ = *p*-CH₃O-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = Me, R₇ = Boc, R₈ = H, Z = N, Y = O) (78.3 mg, 0.172 mmol) and *p*-TsOH (36 mg, 0.189 mmol) in benzene (10 ml) is refluxed for 30 min, then 8 ml of solvent were distilled off. The resulting solution was concentrated obtaining compound I (I wherein R₁ = Ph, R₂ = H, R₃ = *p*-CH₃O-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = Me, X = O, Z = N, Y = O) as *p*-TsOH salt (60 mg, 76%). This was treated with 0.1 M aqueous solution of KOH and the free amine extracted with CHCl₃ to give, after concentration, compound I (I wherein R₁ = Ph, R₂ = H, R₃ = *p*-CH₃O-C₆H₄CH₂, R₄ = H, R₅ = H, R₆ = Me, X = O, Z = N, Y = O) as a colorless oil (41 mg, 70%).

¹H NMR (CDCl₃) δ 7.70 (m, 2 H), 7.52-7.20 (m, 5 H), 6.83 (m, 2 H), 5.07 (s, 1 H), 4.79 (d, *J* = 14.1 Hz, 1 H), 4.55 (d, *J* = 14.1 Hz, 1 H), 3.78 (s, 3 H), 3.76 (m, 2 H), 2.84 (q, *J* = 7.4 Hz, 1 H), 1.60 (d, *J* = 7.4 Hz, 3 H).

EXAMPLE 13

Preparation of (1*S*,5*S*,7*S*)-3-benzyl-5-phenyl-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane [compound I wherein R₁ = Ph, R₂ = H, R₃ = PhCH₂, R₄ = H, R₅ = H, R₆ = CH₂OH, X = H, Z = O, Y = O]

To a suspension of LiAlH₄ (50 mg, mmol) in anhydrous THF (10 mL) was added dropwise at 0 °C and under nitrogen atmosphere a solution of compound I, [prepared according the example 2, wherein R₁ = Ph, R₂ = H, R₃ = PhCH₂, R₄ = H, R₅ = H, R₆ = COOMe, X = O, Z = O, Y = O] (22 mg, 0.568 mmol) in dry THF (12 ml). The mixture was refluxed for 2h, and then, after cooling to 0 °C, diethyl

ether (2 mL) were added. The mixture was filtered through a short layer of anhydrous Na_2SO_4 , and the residue was suspended in 1 M KOH solution (30 mL), saturated with NaCl, and extracted with Et_2O and EtOAc. The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated to give

- 5 compound I (wherein $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{PhCH}_2$, $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{CH}_2\text{OH}$, $\text{X} = \text{H}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$) as a colorless oil (35 mg, 0.112 mmol, 79 %).

^1H NMR (CDCl_3) δ 7.53-7.30 (m, 2 H), 7.29-7.23 (m, 8 H), 4.66-4.34 (m, 2 H), 3.34-3.46 (m, 4 H), 3.06-2.43 (m, 4 H), 1.82 (br s, 1 H).

EXAMPLE 14

- 10 Preparation of Methyl (1*R*,5*S*,7*R*)-3-[(1*S*)-1-carbomethoxy-2-phenylethyl]-2-oxo-5-phenyl-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-exo-carboxylate

[compound I wherein $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{CH}(\text{COOMe})\text{CH}_2\text{Ph}$, $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOMe}$, $\text{X} = \text{O}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$]

Fmoc-(*S*)-phenylalanine-O-Wang resin (2 g, 200-400 mesh, substitution 1 mmol/g)

- 15 was treated with piperidine (30%) in DMF (10 mL) under stirring, for 15 min, to obtain compound VI [wherein $\text{R}_3 = \text{CH}(\text{COO-Wang resin})\text{CH}_2\text{Ph}$]. After filtration, the resin suspended in DMF (10 mL), was treated with 2-bromo-acetophenone (compound V wherein Hal = Br, $\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$), (1.09 g, 6.0 mmol) and DIPEA (340 μL , 2 mmol) and left under stirring at room temperature for 48 h. The resin II

- 20 [$\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{CH}(\text{COO-Wang resin})\text{CH}_2\text{Ph}$] obtained was washed as reported in example 6 with DMF, CH_2Cl_2 , MeOH and again DMF. Resin II [$\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{CH}(\text{COO-Wang resin})\text{CH}_2\text{Ph}$] was then coupled with III [wherein $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOMe}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$, $\text{R}_7\text{---R}_8 = \text{CH}_2\text{---CH}_2$] as follows: compound III (816 mg, 4 mmol) and PyBroP (1.86 g, 4 mmol) were added to resin II (1.00 g)

- 25 suspended in DMF (10 mL), then DIPEA (680 μL , 4 mmol) was added slowly at room temperature and the resulting suspension stirred for 12 h. After the usual work-up, resin IV [$\text{R}_1 = \text{Ph}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{CH}(\text{COO-Wang resin})\text{CH}_2\text{Ph}$, $\text{R}_4 = \text{H}$, $\text{R}_5 = \text{H}$, $\text{R}_6 = \text{COOMe}$, $\text{Z} = \text{O}$, $\text{Y} = \text{O}$, $\text{R}_7\text{---R}_8 = \text{CH}_2\text{---CH}_2$] was obtained. The cyclization step was performed on 1 g of resin IV as follows: resin IV (1 g) and *p*-TsOH (95 mg)

- 30 were suspended in toluene and the mixture refluxed for 15 min. Then part of the solvent (50 mL) was distilled off and the residual suspension filtered. The solution

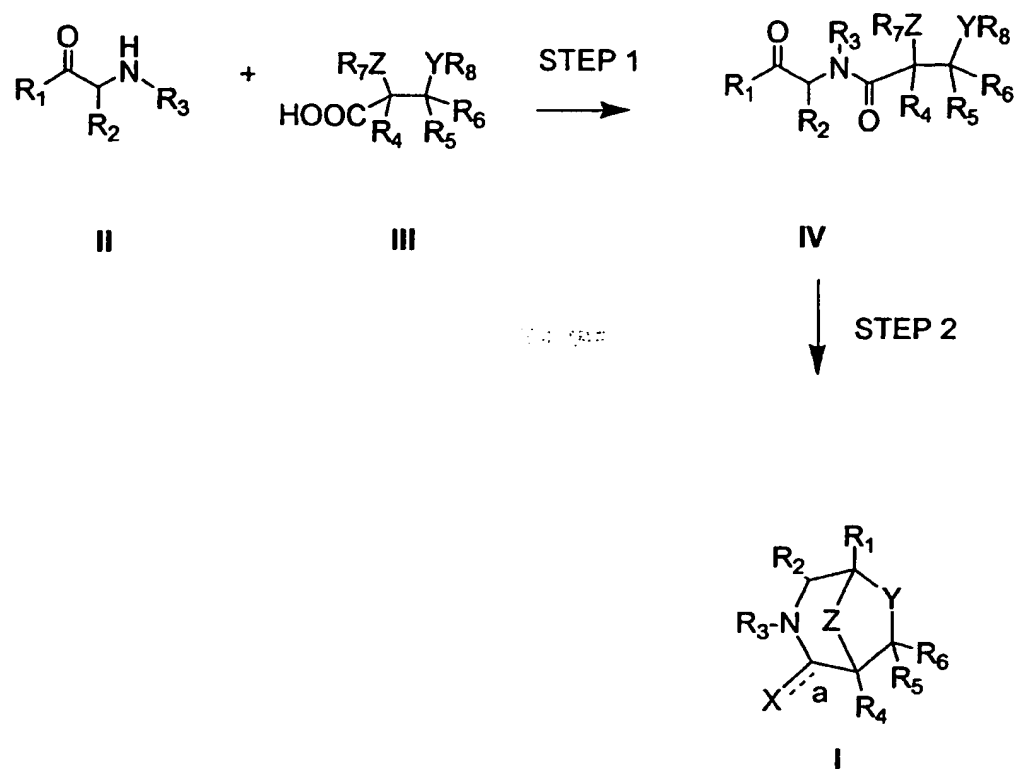
was concentrated obtaining, a solid residue (170 mg) containing compound I [wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOH})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOH}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$]. Alternatively, resin IV was treated in methylene chloride with an equal volume of trifluoroacetic acid (TFA) and water in a 95:5 TFA/water ratio at

5 room temperature for 30 min.

Crude compound I [wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOH})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOH}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$] treated with solution of diazomethane in ether gave compound I [wherein $R_1 = \text{Ph}$, $R_2 = \text{H}$, $R_3 = \text{CH}(\text{COOMe})\text{CH}_2\text{Ph}$, $R_4 = \text{H}$, $R_5 = \text{H}$, $R_6 = \text{COOMe}$, $X = \text{O}$, $Z = \text{O}$, $Y = \text{O}$] identical with the product

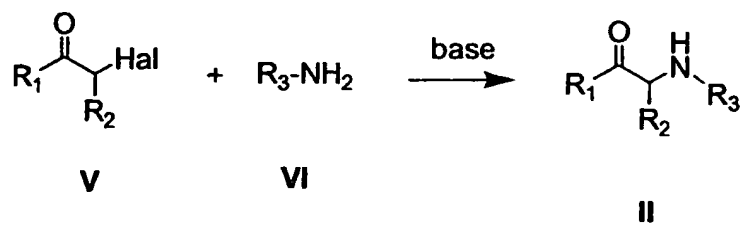
10 (major epimer) as described in example 9.

Scheme 1



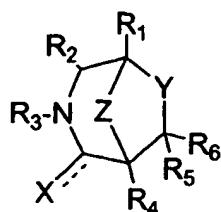
Scheme 2

5



Claims

1. Heterobicycle derivatives of general formula (I)



I

wherein:

- 5 R_1 , is chosen in the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; $RR'N-C_{1-8}$ alkyl, $RR'N$ -aryl, RO -aryl, $R(O)C$ -aryl, $RO(O)C$ -aryl, $RR'N(O)C$ -aryl, (P)-W-NR-aryl, (P)-W-O-aryl, (P)-W-C(O)O-aryl, (P)-W-O(O)C-aryl, (P)-W-C(O)RN-aryl, (P)-W-NR(O)C-aryl;
- R_2 , is chosen in the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; amino C_{1-8} alkyl, aminoaryl, C_{1-8} alkyloxyaryl, hydroxyaryl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl, -
- 10 (side chain), -(side chain)-W-(P) or
- R_1 and R_2 taken together are a C_{1-4} alkyl, C_{2-4} alkenyl, cycloalkyl, benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms;
- 15 R_3 , is chosen in the group consisting H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; $RR'NC_{1-8}$ alkyl, $RR'N$ aryl, $RO-C_{1-8}$ alkyl, $RO(O)C-C_{1-8}$ alkyl, $R(O)C-C_{1-8}$ alkyl, $RC(O)O-C_{1-8}$ alkyl, $RC(O)N(R)C_{1-8}$ alkyl RO -aryl, $RO(O)C$ -aryl, $R(O)C$ -aryl $RC(O)O$ -aryl, $RC(O)N(R)$ aryl, -CH(amino acid side-chain) CO_2R , -CH(amino acid side-chain) $C(O)NR$, -CH(amino acid side-chain)-
- 20 $C(O)O$ -W-(P), -CH(amino acid side-chain)- $C(O)N(R)$ -W-(P), $CH(CO_2R)$ -amino acid side-chain-W-(P), $CH(CONRR')$ -amino acid side-chain-W-(P), protecting group;
- R_4 and R_5 , same or different, are chosen in the group consisting H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl;
- R_6 is chosen in the group consisting, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle, heterocycle C_{1-8} alkyl; - $C(O)R$, - $C(O)OR$, - $C(O)NRR'$, CH_2OR , CH_2NRR' , - $C(O)NH$ -CH(amino acid side-chain) $C(O)OR$, - $C(O)O$ -W-(P), - $C(O)N(R)$ -W-(P), - CH_2O -W-(P), - $CH_2N(R)$ -W-(P);
- 25

R and R', same or different, are chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkinyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; heterocycleC₁₋₈alkyl; a protecting group, -C(O)CH(amino acid side-chain)-NHR, -NH-CH(amino acid side-chain)COOR, -CH(amino acid side-chain)COOR;

5 P is resin, both soluble or bound to a solid support;

W is as linker;

X is O, S, when a is a double bond, or X is H and a is single bond,

Y and Z, same or different, are O, S, SO, SO₂, N-R, wherein R is as above defined;

10 the above said alkyl-, alkenyl-, alkynyl-, cycloalkyl-, aryl- and heterocycle-groups, being possibly substituted.

2. Heterobicycle derivatives according to Claim 1 wherein:

the resin P is a polymeric material soluble in the solvents commonly used in organic synthesis or bound to a solid support;

15 the solid support is a solid material (at room temperature) to which starting resin materials (reactive groups) may be bound;

W is a molecule capable of binding the resin P to the reagents and the products of formula (I);

20 Protecting group means any group capable of preventing the atom to which it is attached from participating in an undesired reaction or bonding, as commonly used in synthesis reactions.

Amino acid side-chain means the side chain moieties of the natural occurring L or D amino acids or the non naturally occurring amino acids;

and the other substituents are as defined in Claim 1.

25 3. Heterobicycle derivatives according to Claim 2 wherein:

the resin is a polymeric material derivatised with a -NH₂ group or an hydroxyl group possibly bound to a solid support materials chosen among polyethylene and polystyrene compounds and related inert polymeric compounds;

30 protecting groups are those which prevent reaction or bonding of oxygen, nitrogen, carboxylic acids, thiols, alcohols, amines and the like;

the amino acid side-chain is the side chain of a naturally or non naturally occurring amino acid and the other substituents are as defined in Claim 1.

4. Heterobicycle derivatives according to Claim 3 wherein the non naturally occurring amino acids are chosen among. norleucine (Nle), norvaline (Nva), β -alanine, L or D α -phenyl glycine and the like and the other substituents are as described in Claim 1.

5. Heterobicycle derivatives according to Claim 4 represented by the following formulae:

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1.	O	O	O	Ph	H	PhCH ₂	H	H	COOH
2.	O	O	O	4-HO-Ph	H	PhCH ₂	H	H	COOH
3.	O	O	O	4-O ₂ N-Ph	H	PhCH ₂	H	H	COOH
4.	O	O	O	4-H ₂ N-Ph	H	PhCH ₂	H	H	COOH
5.	O	O	O	4-MeO(O)C-Ph	H	PhCH ₂	H	H	COOH
6.	O	O	O	4-Me-Ph	H	PhCH ₂	H	H	COOH
7.	O	O	O	4-MeO-Ph	H	PhCH ₂	H	H	COOH
8.	O	O	O	4-Cl-Ph	H	PhCH ₂	H	H	COOH
9.	O	O	O	4-Br-Ph	H	PhCH ₂	H	H	COOH
10.	O	O	O	2-HO-Ph	H	PhCH ₂	H	H	COOH
11.	O	O	O	2-O ₂ N-Ph	H	PhCH ₂	H	H	COOH
12.	O	O	O	2-H ₂ N-Ph	H	PhCH ₂	H	H	COOH
13.	O	O	O	2-MeO(O)C-Ph	H	PhCH ₂	H	H	COOH
14.	O	O	O	2-Me-Ph	H	PhCH ₂	H	H	COOH
15.	O	O	O	2-MeO-Ph	H	PhCH ₂	H	H	COOH
16.	O	O	O	2-Cl-Ph	H	PhCH ₂	H	H	COOH
17.	O	O	O	2-Br-Ph	H	PhCH ₂	H	H	COOH
18.	O	O	O	2-Nafthyl	H	PhCH ₂	H	H	COOH
19.	O	O	O	2-thienyl	H	PhCH ₂	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
20.	O	O	O	4-biphenyl	H	PhCH ₂	H	H	COOH
21.	O	O	O	Ph	H	Me	H	H	COOH
22.	O	O	O	Ph	H	CH ₃ (CH ₂) ₂	H	H	COOH
23.	O	O	O	Ph	H	cyclohexyl	H	H	COOH
24.	O	O	O	Ph	H	allyl	H	H	COOH
25.	O	O	O	Ph	H	Ph	H	H	COOH
26.	O	O	O	Ph	H	4-HO-Ph	H	H	COOH
27.	O	O	O	Ph	H	4-O ₂ N-Ph	H	H	COOH
28.	O	O	O	Ph	H	4-MeO ₂ C-Ph	H	H	COOH
29.	O	O	O	Ph	H	4-Me-Ph	H	H	COOH
30.	O	O	O	Ph	H	4-MeO-Ph	H	H	COOH
31.	O	O	O	Ph	H	4-Cl-Ph	H	H	COOH
32.	O	O	O	Ph	H	4-Br-Ph	H	H	COOH
33.	O	O	O	Ph	H	2-HO-Ph	H	H	COOH
34.	O	O	O	Ph	H	2-O ₂ N-Ph	H	H	COOH
35.	O	O	O	Ph	H	2-MeO ₂ C-Ph	H	H	COOH
36.	O	O	O	Ph	H	2-Me-Ph	H	H	COOH
37.	O	O	O	Ph	H	2-MeO-Ph	H	H	COOH
38.	O	O	O	Ph	H	2-Cl-Ph	H	H	COOH
39.	O	O	O	Ph	H	2-Br-Ph	H	H	COOH
40.	O	O	O	Ph	H	2-Nafthyl	H	H	COOH
41.	O	O	O	Ph	H	2-thienyl	H	H	COOH
42.	O	O	O	Ph	H	4-biphenyl	H	H	COOH
43.	O	O	O	Ph	H	4-MeO ₂ C-PhCH ₂	H	H	COOH
44.	O	O	O	Ph	H	4-Me-PhCH ₂	H	H	COOH
45.	O	O	O	Ph	H	4-MeOPhCH ₂	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
46.	O	O	O	Ph	H	4-Cl-PhCH ₂	H	H	COOH
47.	O	O	O	Ph	H	4-Br-PhCH ₂	H	H	COOH
48.	O	O	O	Ph	H	2-HO-PhCH ₂	H	H	COOH
49.	O	O	O	Ph	H	2-O ₂ N-PhCH ₂	H	H	COOH
50.	O	O	O	Ph	H	2-MeO ₂ C-PhCH ₂	H	H	COOH
51.	O	O	O	Ph	H	2-Me-PhCH ₂	H	H	COOH
52.	O	O	O	Ph	H	2-MeO-PhCH ₂	H	H	COOH
53.	O	O	O	Ph	H	2-Cl-PhCH ₂	H	H	COOH
54.	O	O	O	Ph	H	2-Br-PhCH ₂	H	H	COOH
55.	O	O	O	4-HO-Ph	H	4-HO-Ph CH ₂	H	H	COOH
56.	O	O	O	4-HO-Ph	H	4-O ₂ N-PhCH ₂	H	H	COOH
57.	O	O	O	4-HO-Ph	H	4-MeO ₂ C-PhCH ₂	H	H	COOH
58.	O	O	O	4-HO-Ph	H	4-Me-PhCH ₂	H	H	COOH
59.	O	O	O	4-HO-Ph	H	4-MeOPhCH ₂	H	H	COOH
60.	O	O	O	4-HO-Ph	H	4-Cl-PhCH ₂	H	H	COOH
61.	O	O	O	4-HO-Ph	H	4-Br-PhCH ₂	H	H	COOH
62.	O	O	O	4-HO-Ph	H	2-HO-PhCH ₂	H	H	COOH
63.	O	O	O	4-HO-Ph	H	2-O ₂ N-PhCH ₂	H	H	COOH
64.	O	O	O	4-HO-Ph	H	2-MeO ₂ C-PhCH ₂	H	H	COOH
65.	O	O	O	4-HO-Ph	H	2-Me-PhCH ₂	H	H	COOH
66.	O	O	O	4-HO-Ph	H	2-MeO-PhCH ₂	H	H	COOH
67.	O	O	O	4-HO-Ph	H	2-Cl-PhCH ₂	H	H	COOH
68.	O	O	O	4-HO-Ph	H	2-Br-PhCH ₂	H	H	COOH
69.	O	O	O	4-HO-Ph	H	Me	H	H	COOH
70.	O	O	O	4-HO-Ph	H	CH ₃ (CH ₂) ₂	H	H	COOH
71.	O	O	O	4-HO-Ph	H	cyclohexyl	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
72.	O	O	O	4-HO-Ph	H	allyl	H	H	COOH
73.	O	O	O	Ph	H	HO ₂ C-CH ₂	H	H	COOH
74.	O	O	O	Ph	H	Bn(HO ₂ C)CH	H	H	COOH
75.	O	O	O	Ph	H	HOCH ₂ (HO ₂ C)CH	H	H	COOH
76.	O	O	O	Ph	H	CH ₃ (HO)CH(HO ₂ C)CH	H	H	COOH
77.	O	O	O	Ph	H	MeS(CH ₂) ₂ (HO ₂ C)CH	H	H	COOH
78.	O	O	O	Ph	H	H ₂ N(CH ₂) ₃ (HO ₂ C)CH	H	H	COOH
79.	O	O	O	Ph	H	HO ₂ CCH ₂ (HO ₂ C)CH	H	H	COOH
80.	O	O	O	Ph	H	imidazole-CH ₂ (HO ₂ C)CH	H	H	COOH
81.	O	O	O	Ph	H	indole-CH ₂ (HO ₂ C)CH	H	H	COOH
82.	O	O	O	4-HO-Ph	H	HO ₂ C-CH ₂	H	H	COOH
83.	O	O	O	4-HO-Ph	H	Me(HO ₂ C)CH	H	H	COOH
84.	O	O	O	4-HO-Ph	H	(CH ₃) ₂ CH(HO ₂ C)CH	H	H	COOH
85.	O	O	O	4-HO-Ph	H	Bn(HO ₂ C)CH	H	H	COOH
86.	O	O	O	4-HO-Ph	H	HOCH ₂ (HO ₂ C)CH	H	H	COOH
87.	O	O	O	4-HO-Ph	H	CH ₃ (HO)CH(HO ₂ C)CH	H	H	COOH
88.	O	O	O	4-HO-Ph	H	MeS(CH ₂) ₂ (HO ₂ C)CH	H	H	COOH
89.	O	O	O	4-HO-Ph	H	H ₂ N(CH ₂) ₃ (HO ₂ C)CH	H	H	COOH
90.	O	O	O	4-HO-Ph	H	HO ₂ CCH ₂ (HO ₂ C)CH	H	H	COOH
91.	O	O	O	4-HO-Ph	H	imidazole-CH ₂ (HO ₂ C)CH	H	H	COOH
92.	O	O	O	4-HO-Ph	H	indole-CH ₂ (HO ₂ C)CH	H	H	COOH
93.	O	O	O	Ph	Me	PhCH ₂	H	H	COOH
94.	O	O	O	4-HO-Ph	Me	PhCH ₂	H	H	COOH
95.	O	O	O	Ph	Bn	PhCH ₂	H	H	COOH
96.	O	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	COOH
97.	O	O	O	Ph	Me	HO ₂ C-CH ₂	H	H	COOH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
98.	O	O	O	4-HO-Ph	Me	HO ₂ C-CH ₂	H	H	COOH
99.	O	O	O	Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
100.	O	O	O	4-HO-Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
101.	O	O	O	Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
102.	O	O	O	4-HO-Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
103.	O	HN	O	Ph	H	PhCH ₂	H	H	CH ₃
104.	O	HN	O	Ph	Me	PhCH ₂	H	H	CH ₃
105.	O	HN	O	Ph	Bn	PhCH ₂	H	H	CH ₃
106.	O	HN	O	4-OH-Ph	H	PhCH ₂	H	H	CH ₃
107.	O	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	CH ₃
108.	O	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	CH ₃
109.	O	HN	O	Ph	H	Ph	H	H	CH ₃
110.	O	HN	O	Ph	Me	Ph	H	H	CH ₃
111.	O	HN	O	Ph	Bn	Ph	H	H	CH ₃
112.	O	HN	O	4-OH-Ph	H	Ph	H	H	CH ₃
113.	O	HN	O	4-OH-Ph	Me	Ph	H	H	CH ₃
114.	O	HN	O	4-OH-Ph	Bn	Ph	H	H	CH ₃
115.	O	HN	O	Ph	H	CH ₃ -Ph	H	H	CH ₃
116.	O	HN	O	Ph	Me	CH ₃ -Ph	H	H	CH ₃
117.	O	HN	O	Ph	Bn	CH ₃ -Ph	H	H	CH ₃
118.	O	HN	O	4-OH-Ph	H	CH ₃ -Ph	H	H	CH ₃
119.	O	HN	O	4-OH-Ph	Me	CH ₃ -Ph	H	H	CH ₃
120.	O	HN	O	4-OH-Ph	Bn	CH ₃ -Ph	H	H	CH ₃
121.	O	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
122.	O	HN	O	Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
123.	O	HN	O	Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
124.	O	HN	O	4-OH-Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
125.	O	HN	O	4-OH-Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
126.	O	HN	O	4-OH-Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
127.	O	HN	O	Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
128.	O	HN	O	Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
129.	O	HN	O	Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
130.	O	HN	O	4-OH-Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
131.	O	HN	O	4-OH-Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
132.	O	HN	O	4-OH-Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
133.	O	HN	O	Ph	H	Me	H	H	CH ₃
134.	O	HN	O	Ph	H	CH ₃ (CH ₂) ₂	H	H	CH ₃
135.	O	HN	O	Ph	H	cyclohexyl	H	H	CH ₃
136.	O	HN	O	Ph	H	allyl	H	H	CH ₃
137.	O	HN	O	4-OH-Ph	H	Me	H	H	CH ₃
138.	O	HN	O	4-OH-Ph	H	CH ₃ (CH ₂) ₂	H	H	CH ₃
139.	O	HN	O	4-OH-Ph	H	cyclohexyl	H	H	CH ₃
140.	O	HN	O	4-OH-Ph	H	allyl	H	H	CH ₃
141.	O	HN	O	Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
142.	O	HN	O	Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
143.	O	HN	O	Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
144.	O	HN	O	4-OH-Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
145.	O	HN	O	4-OH-Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
146.	O	HN	O	4-OH-Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
147.	O	HN	O	Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
148.	O	HN	O	Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
149.	O	HN	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
150.	O	HN	O	4-OH-Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
151.	O	HN	O	4-OH-Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
152.	O	HN	O	4-OH-Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
153.	H	O	O	Ph	H	PhCH ₂	H	H	COOH
154.	H	O	O	Ph	Me	PhCH ₂	H	H	COOH
155.	H	O	O	Ph	Bn	PhCH ₂	H	H	COOH
156.	H	O	O	4-HO-Ph	H	PhCH ₂	H	H	COOH
157.	H	O	O	4-HO-Ph	Me	PhCH ₂	H	H	COOH
158.	H	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	COOH
159.	H	O	O	Ph	H	HO ₂ C-CH ₂	H	H	COOH
160.	H	O	O	Ph	Me	HO ₂ C-CH ₂	H	H	COOH
161.	H	O	O	Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
162.	H	O	O	4-HO-Ph	H	HO ₂ C-CH ₂	H	H	COOH
163.	H	O	O	4-HO-Ph	Me	HO ₂ C-CH ₂	H	H	COOH
164.	H	O	O	4-HO-Ph	Bn	HO ₂ C-CH ₂	H	H	COOH
165.	H	O	O	Ph	H	Bn(HO ₂ C)CH	H	H	COOH
166.	H	O	O	Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
167.	H	O	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	COOH
168.	H	O	O	4-HO-Ph	H	Bn(HO ₂ C)CH	H	H	COOH
169.	H	O	O	4-HO-Ph	Me	Bn(HO ₂ C)CH	H	H	COOH
170.	H	O	O	4-HO-Ph	Bn	Bn(HO ₂ C)CH	H	H	COOH
171.	H	HN	O	Ph	H	PhCH ₂	H	H	CH ₃
172.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
173.	H	HN	O	Ph	Me	PhCH ₂	H	H	CH ₃
174.	H	HN	O	Ph	Bn	PhCH ₂	H	H	CH ₃
175.	H	HN	O	4-OH-Ph	H	PhCH ₂	H	H	CH ₃

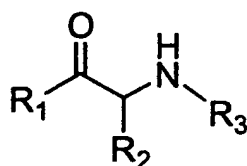
Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
176.	H	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	CH ₃
177.	H	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	CH ₃
178.	H	HN	O	Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
179.	H	HN	O	Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
180.	H	HN	O	Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
181.	H	HN	O	4-OH-Ph	H	HO ₂ C-CH ₂	H	H	CH ₃
182.	H	HN	O	4-OH-Ph	Me	HO ₂ C-CH ₂	H	H	CH ₃
183.	H	HN	O	4-OH-Ph	Bn	HO ₂ C-CH ₂	H	H	CH ₃
184.	H	HN	O	Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
185.	H	HN	O	Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
186.	H	HN	O	Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
187.	H	HN	O	4-OH-Ph	H	Bn(HO ₂ C)CH	H	H	CH ₃
188.	H	HN	O	4-OH-Ph	Me	Bn(HO ₂ C)CH	H	H	CH ₃
189.	H	HN	O	4-OH-Ph	Bn	Bn(HO ₂ C)CH	H	H	CH ₃
190.	H	HN	O	Ph	H	Ph	H	H	CH ₃
191.	H	HN	O	Ph	Me	Ph	H	H	CH ₃
192.	H	HN	O	Ph	Bn	Ph	H	H	CH ₃
193.	H	HN	O	4-OH-Ph	H	Ph	H	H	CH ₃
194.	H	HN	O	4-OH-Ph	Me	Ph	H	H	CH ₃
195.	H	HN	O	4-OH-Ph	Bn	Ph	H	H	CH ₃
196.	H	HN	O	Ph	H	CH ₃ -Ph	H	H	CH ₃
197.	H	HN	O	Ph	Me	CH ₃ -Ph	H	H	CH ₃
198.	H	HN	O	Ph	Bn	CH ₃ -Ph	H	H	CH ₃
199.	H	HN	O	4-OH-Ph	H	CH ₃ -Ph	H	H	CH ₃
200.	H	HN	O	4-OH-Ph	Me	CH ₃ -Ph	H	H	CH ₃
201.	H	HN	O	4-OH-Ph	Bn	CH ₃ -Ph	H	H	CH ₃

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
202.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
203.	H	HN	O	Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
204.	H	HN	O	Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
205.	H	HN	O	4-OH-Ph	H	4-MeO-PhCH ₂	H	H	CH ₃
206.	H	HN	O	4-OH-Ph	Me	4-MeO-PhCH ₂	H	H	CH ₃
207.	H	HN	O	4-OH-Ph	Bn	4-MeO-PhCH ₂	H	H	CH ₃
208.	H	HN	O	Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
209.	H	HN	O	Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
210.	H	HN	O	Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
211.	H	HN	O	4-OH-Ph	H	CH ₃ -PhCH ₂	H	H	CH ₃
212.	H	HN	O	4-OH-Ph	Me	CH ₃ -PhCH ₂	H	H	CH ₃
213.	H	HN	O	4-OH-Ph	Bn	CH ₃ -PhCH ₂	H	H	CH ₃
214.	H	O	O	Ph	H	PhCH ₂	H	H	CH ₂ OH
215.	H	O	O	Ph	H	4-MeOPhCH ₂	H	H	CH ₂ OH
216.	H	O	O	Ph	Me	PhCH ₂	H	H	CH ₂ OH
217.	H	O	O	Ph	Bn	PhCH ₂	H	H	CH ₂ OH
218.	H	O	O	4-HO-Ph	H	PhCH ₂	H	H	CH ₂ OH
219.	H	O	O	4-HO-Ph	Me	PhCH ₂	H	H	CH ₂ OH
220.	H	O	O	4-HO-Ph	Bn	PhCH ₂	H	H	CH ₂ OH
221.	H	O	O	Ph	H	HOCH ₂	H	H	CH ₂ OH
222.	H	O	O	Ph	Me	HOCH ₂	H	H	CH ₂ OH
223.	H	O	O	Ph	Bn	HOCH ₂	H	H	CH ₂ OH
224.	H	O	O	4-HO-Ph	H	HOCH ₂	H	H	CH ₂ OH
225.	H	O	O	4-HO-Ph	Me	HOCH ₂	H	H	CH ₂ OH
226.	H	O	O	4-HO-Ph	Bn	HOCH ₂	H	H	CH ₂ OH
227.	H	O	O	Ph	H	Bn(HOH ₂ C)CH	H	H	CH ₂ OH

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
228.	H	O	O	Ph	Me	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
229.	H	O	O	Ph	Bn	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
230.	H	O	O	4-HO-Ph	H	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
231.	H	O	O	4-HO-Ph	Me	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
232.	H	O	O	4-HO-Ph	Bn	Bn(HOH ₂ C)CH	H	H	CH ₂ OH
233.	H	HN	O	Ph	H	PhCH ₂	H	H	H
234.	H	HN	O	Ph	H	4-MeO-PhCH ₂	H	H	H
235.	H	HN	O	Ph	Me	PhCH ₂	H	H	H
236.	H	HN	O	Ph	Bn	PhCH ₂	H	H	H
237.	H	HN	O	4-OH-Ph	H	PhCH ₂	H	H	H
238.	H	HN	O	4-OH-Ph	Me	PhCH ₂	H	H	H
239.	H	HN	O	4-OH-Ph	Bn	PhCH ₂	H	H	H
240.	H	HN	O	Ph	H	HOCH ₂	H	H	H
241.	H	HN	O	Ph	Me	HOCH ₂	H	H	H
242.	H	HN	O	Ph	Bn	HOCH ₂	H	H	H
243.	H	HN	O	4-OH-Ph	H	HOCH ₂	H	H	H
244.	H	HN	O	4-OH-Ph	Me	HOCH ₂	H	H	H
245.	H	HN	O	4-OH-Ph	Bn	HOCH ₂	H	H	H
246.	H	HN	O	Ph	H	Bn(HOH ₂ C)CH	H	H	H
247.	H	HN	O	Ph	Me	Bn(HOH ₂ C)CH	H	H	H
248.	H	HN	O	Ph	Bn	Bn(HOH ₂ C)CH	H	H	H
249.	H	HN	O	4-OH-Ph	H	Bn(HOH ₂ C)CH	H	H	H
250.	H	HN	O	4-OH-Ph	Me	Bn(HOH ₂ C)CH	H	H	H
251.	H	HN	S	Ph	H	PhCH ₂	H	H	H
252.	H	HN	S	Ph	H	4-MeO-PhCH ₂	H	H	H
253.	H	HN	S	Ph	Me	PhCH ₂	H	H	H

Comp.	X	Z	Y	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
254.	H	HN	S	Ph	Bn	PhCH ₂	H	H	H
255.	H	HN	S	4-OH-Ph	H	PhCH ₂	H	H	H
256.	H	HN	S	4-OH-Ph	Me	PhCH ₂	H	H	H
257.	H	HN	S	4-OH-Ph	Bn	PhCH ₂	H	H	H
258.	H	HN	S	Ph	H	HOCH ₂	H	H	H
259.	H	HN	S	Ph	Me	HOCH ₂	H	H	H
260.	H	HN	S	Ph	Bn	HOCH ₂	H	H	H
261.	H	HN	S	4-OH-Ph	H	HOCH ₂	H	H	H
262.	H	HN	S	4-OH-Ph	Me	HOCH ₂	H	H	H
263.	H	HN	S	4-OH-Ph	Bn	HOCH ₂	H	H	H
264.	H	HN	S	Ph	H	Bn(HOH ₂ C)CH	H	H	H
265.	H	HN	S	Ph	Me	Bn(HOH ₂ C)CH	H	H	H
266.	H	HN	S	Ph	Bn	Bn(HOH ₂ C)CH	H	H	H
267.	H	HN	S	4-OH-Ph	H	Bn(HOH ₂ C)CH	H	H	H
268.	H	HN	S	4-OH-Ph	Me	Bn(HOH ₂ C)CH	H	H	H

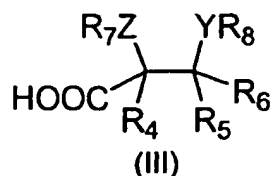
6. Process for the preparation of compounds of formula (I) according to Claim 1 wherein a compound of formula (II)



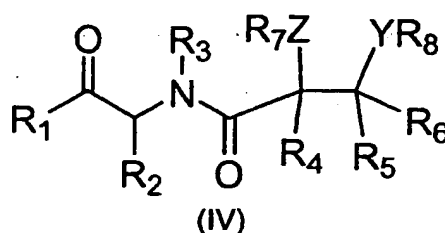
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II

wherein R₁, R₂, R₃, are as above defined
is reacted with a compound of formula (III)



wherein R_4 , R_5 , R_6 , Y and Z are as above defined and R_7 , R_8 represent H or suitable protecting groups, (Pg) which can be same or different, cyclic or acyclic, and which can be cleaved in acidic conditions, in order to give a compound of formula (IV)



wherein the substituents have the meaning as above, which is cyclised to a compound of formula (I) by action of an acid.

- 10 7. Process according to Claim 5 wherein the first step is performed in an aprotic polar solvent at a temperature comprised between 0 – 100°C for 1 – 24 hours.
8. Process according to Claim 6 wherein the reaction is performed in the presence of a coupling agent.
9. Process according to Claim 5 wherein the second step is performed in the presence of a strong acid at a temperature of 0°-150°C for 15min – 24 hours
- 15 10. Process according to Claim 8 wherein the acid is chosen in the group consisting of: sulphuric acid adsorbed on silica gel, p-toluen sulphonic acid, trifluoroacetic acid, trifluorometansulphonic acid.
11. Libraries consisting of compounds of formula (I) according to Claim 1.
- 20 12. Generation of combinatorial libraries according to Claim 10 in mixture synthesis, split and recombine synthesis and parallel synthesis either in manual or automated fashion.
13. Use of compounds of formula 1 for the preparation of new leads for therapeutical applications.

14. Use of libraries consisting of compounds of formula 1 for the preparation of new leads for therapeutical applications.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/02185

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/08 //(C07D498/08,317:00,265:00),(C07D498/08,263:00,241:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 892 853 A (DELALANDE S.A.) 15 October 1982 (1982-10-15) claims 1-4	1-4
X	J.-Q. WANG, W.-S. TIAN: J. CHEM. SOC. PERKIN TRANS. 1, no. 2, 1996, pages 209-212, XP002142445 * Compound of formula 12 * page 210, right-hand column -/-	1-4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

4 May 2001

Date of mailing of the international search report

11/05/2001

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/02185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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